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# Tracking of lung function from 10 to 35 years after being born extremely preterm or with extremely low birth weight

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## ABSTRACT

**Background** Lifelong pulmonary consequences of being born extremely preterm or with extremely low birth weight remain unknown. We aimed to describe lung function trajectories from 10 to 35 years of age for individuals born extremely preterm, and address potential cohort effects over a period that encompassed major changes in perinatal care.

**Methods** We performed repeated spirometry in three population-based cohorts born at gestational age  $\leq 28$  weeks or with birth weight  $\leq 1000$  g during 1982–85, 1991–92 and 1999–2000, referred to as extremely preterm-born, and in term-born controls matched for age and gender. Examinations were performed at 10, 18, 25 and 35 years. Longitudinal data were analysed using mixed models regression, with the extremely preterm-born stratified by bronchopulmonary dysplasia (BPD).

**Results** We recruited 148/174 (85%) eligible extremely preterm-born and 138 term-born. Compared with term-born, the extremely preterm-born had lower z-scores for forced expiratory volume in 1 s ( $FEV_1$ ) at most assessments, the main exceptions were in the groups without BPD in the two youngest cohorts.  $FEV_1$  trajectories were largely parallel for the extremely preterm- and term-born, also during the period 25–35 years that includes the onset of the age-related decline in lung function. Extremely preterm-born had lower peak lung function than term-born, but z- $FEV_1$  values improved for each consecutive decade of birth ( $p=0.009$ ). More extremely preterm—than term-born fulfilled the spirometry criteria for chronic obstructive pulmonary disease, 44/148 (30%) vs 7/138 (5%),  $p<0.001$ .

**Conclusions** Lung function after extremely preterm birth tracked in parallel, but significantly below the trajectories of term-born from 10 to 35 years, including the incipient age-related decline from 25 to 35 years. The deficits versus term-born decreased with each decade of birth from 1980 to 2000.

## INTRODUCTION

Rarely in the history of medicine were the ‘frontiers of the possible’ pushed further and faster than in our neonatal intensive care units (NICU) during the 1980s and 1990s.<sup>1</sup> By the turn of the millennium, survival approached 80%–90% for 28 weeks’ gestation, the cut-off for being labelled extremely

## Key messages

### What is already known on this topic?

⇒ Extremely premature birth is associated with airway obstruction during childhood, adolescence and young adulthood. Survival was uncommon in these infants before the 1980s and their lifetime health prospects are therefore unknown.

### What this study adds?

⇒ This is the first population-based longitudinal study to describe lung function trajectories well into adulthood in extremely preterm-born survivors, describing persistent airway obstruction beyond peak function in early adult life and throughout the onset of the age-related decline from 25 to 35 years.

### How this study might affect research, practice and/or policy?

⇒ Chronic obstructive pulmonary disease roots in early life, and extremely premature birth represents an important precursor that needs to be acknowledged by chest physicians and targeted by the research community.

premature.<sup>2</sup> In high-income countries, extremely preterm-born infants currently account for one in 200 children growing up.<sup>3</sup> They are born at a time when the lungs normally undergo complex developmental processes in a protected intrauterine environment. In contrast, the lungs of infants born at this early stage are exposed to lifesaving, but also harmful, intensive care. Survivors are at increased risk of chronic lung disease as well as premature death from a range of causes.<sup>4</sup>

Lung function normally increases through childhood and adolescence, reaches a peak in the mid-20s, and then gradually declines with age.<sup>5</sup> The trajectory is modulated by genetic mechanisms, antenatal factors, and multiple early events and exposures.<sup>6</sup> For most people, the adult decline proceeds unrecognised as symptoms only appear if lung function reaches very low levels.<sup>7</sup> For infants born extremely preterm, this lifespan perspective represents uncharted territory, as their high survival rates are recent achievements.



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Most extremely preterm-born do not appear to reach their expected peak adult lung function.<sup>8</sup> A few longitudinal studies have traced their lung function up to the mid-20s, finding both deterioration or tracking in parallel although at lower levels, when compared with subjects born at term.<sup>9–13</sup> To date, no longitudinal studies have traced lung function of extremely preterm-born past 25 years of age, and thus we lack information regarding the nature of their age-related decline. Given their common early morbidities, the decline might start at a younger age or be steeper than in the general population, and early chronic obstructive pulmonary disease (COPD) is a feared scenario.<sup>14</sup> Bronchopulmonary dysplasia (BPD) is a respiratory complication affecting approximately 50% of extremely preterm-born neonates, primarily characterised by prolonged requirement for supplemental oxygen in the neonatal period.<sup>2</sup> BPD is associated with subsequent airway obstruction and bronchial hyper-responsiveness, and there are concerns for additional negative impact on adult pulmonary health.<sup>5 14</sup>

We have previously reported lung function data from three population-based cohorts born extremely preterm or with extremely low birth weight (BW) (hereafter referred to as extremely preterm-born) during the early 1980s, 1990s and 2000s.<sup>12 15 16</sup> With the present extension of these studies, we aimed to describe their lung function trajectories well into adulthood, and to address potential cohort effects over almost twenty years of inclusion, a period that encompassed major changes in perinatal care. We hypothesised that lung function in subjects born extremely preterm tracked in parallel, but below the level of matched term-born controls, and that differences decreased with succeeding decade of birth.

## MATERIAL AND METHODS

### Subjects and study design

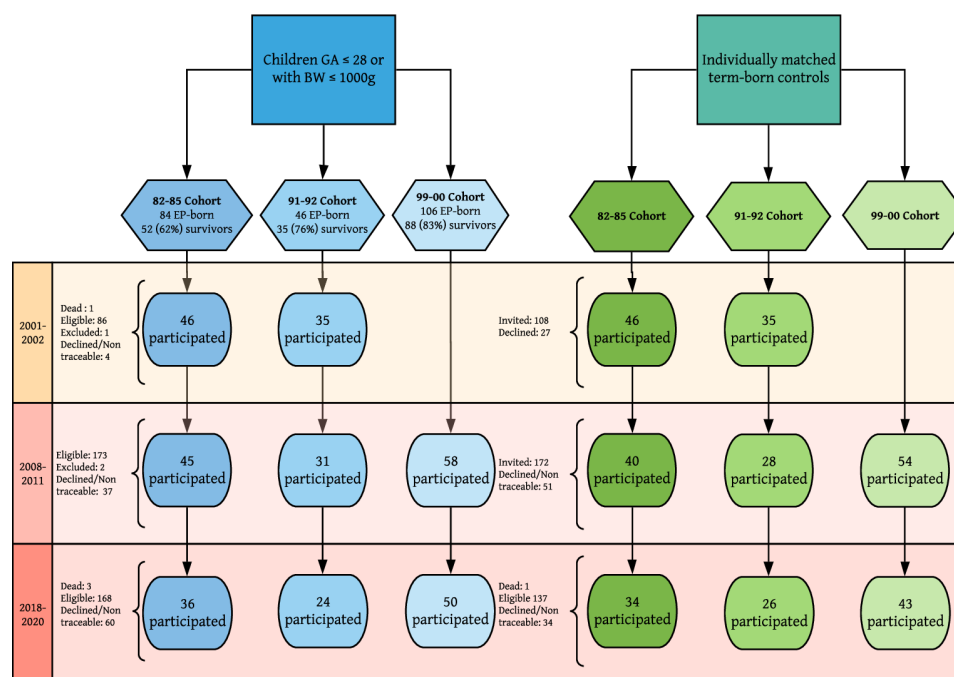
Three regional population-based cohorts born during 1982–1985 (82–85 cohort), 1991–1992 (91–92 cohort) and 1999–2000 (99–00 cohort) at gestational age (GA)  $\leq 28$  (82–85

and 91–92 cohort) or  $\leq 27$  weeks (99–00 cohort), or with BW  $\leq 1000$  g were included. For each extremely preterm-born, the temporally closest individual born at term at the same hospital and of the same sex with BW 3–4 kg (Norwegian 10–90 percentiles)<sup>17</sup> was recruited as a control. The cohorts were assessed at three (two for the 99–00 cohort) study-visits performed in 2001–2002, 2008–2011 and 2018–2020 at, respectively, 18, 25 and 35 years; 10, 18 and 25 years; and 10 and 18 years (figure 1). Inclusion and study design has been described previously.<sup>12 15 16</sup> The subjects completed the International Study of Asthma and Allergy in Childhood<sup>18</sup> questionnaire at each visit.

BPD was defined as need for supplemental oxygen or respiratory support at postmenstrual age  $\geq 36$  weeks. The mode of determination of GA, and the definitions of small for GA (SGA), smoking status, atopy and asthma have been described previously,<sup>12 15 16</sup> and is also provided in the online supplemental file.

### Lung function measurements

Spirometry without prior administration of bronchodilator was performed and reviewed according to standard criteria<sup>19</sup> in a lung physiology laboratory with experienced test-personnel, using a Vmax spirometer (SensorMedics, Anaheim, California, USA) for the first two study visits, and a Vyntus pneumo spirometer (Vyair, Hoechst, Germany) for the last. Forced expiratory volume in 1 s ( $FEV_1$ ), forced vital capacity (FVC), the ratio  $FEV_1/FVC$  and forced expiratory flow at 25%–75% of FVC ( $FEF_{25-75\%}$ ) were recorded. Raw data were normalised for age, sex, ethnicity and height.<sup>20</sup> The lower limit of normal (LLN) was defined as z-score  $\leq -1.645$ . The Global lung function initiative (GLI) equations were used to estimate peak expected lung function at 20 and 22 years for females and males, respectively, defining participants' final height as measured at 18 or 25 years, whichever was highest. The spirometry criteria for COPD was defined as  $FEV_1/FVC$  z-score  $\leq LLN$ .



**Figure 1** Patient inclusion. The inclusion procedure for the extremely preterm (EP)-born (born at gestational age  $\leq 28$  weeks or birth weight  $\leq 1000$  g) and their matched term-born controls. BW, Birth weight; GA, gestational age.

## Statistical methods

Descriptive data are reported as means, SD, ranges, counts and/or percentages, as appropriate. Questionnaire data are presented as at least one positive response at any visit. Welch's one-way analysis of variance (ANOVA)/t-tests, Kruskal-Wallis, Wilcoxon-Mann-Whitney and Pearson's  $\chi^2$  tests, were performed to compare exposure variables between cohorts and between extremely preterm and term-born subjects within cohorts, as appropriate. We fitted linear mixed-effects longitudinal models to estimate, for each time point, mean z-scores for FEV<sub>1</sub>, FVC, FEV<sub>1</sub>/FVC and FEF<sub>25-75%</sub> and FEV<sub>1</sub> as percentage of expected adult peak. The explanatory variables were cohort, age group and subject category (term-born vs extremely preterm-born without BPD vs extremely preterm-born with BPD). For maximal flexibility, all possible interactions of these explanatory variables were included, and subjects were included as a random intercept. The use of mixed-effects models allows inclusion of subjects with incomplete follow-up data, reduces bias caused by missing data, and increases the precision of the estimates.<sup>21</sup>

We fitted simplified versions of the full model to test for cohort effects and parallel longitudinal patterns, and we compared the full and simplified models using likelihood ratio tests. To compare cohorts of extremely preterm-born subjects, we omitted the age variable, as FEV<sub>1</sub> z-scores were stable over time. To assess the effects of neonatal variables, we fitted a multiple regression model for z-FEV<sub>1</sub> at 18 years, the only age where all cohorts had measurements. Explanatory variables were cohort, BPD status, GA, BW z-score, maternal smoking and treatment with surfactant and antenatal steroids. We evaluated the effect of current smoking at 18 years on z-FEV<sub>1</sub> for the 82–85 and 91–92 cohorts by Welch's t-test (data missing for the 99–00 cohort).

All models were fitted using R V.4.0.2, and the mixed-effects models by using the R package 'lme4' V.1.1–25. Values of  $p \leq 0.05$  were characterised as statistically significant.

The study was originally designed in 2001 to have 90% power to detect differences exceeding 7.5 percentage points in FEV<sub>1</sub> between the extremely preterm-born and term-born groups, given normally distributed data, a within-group SD of 10 percentage points, and a two-sided significance level of 0.05. This required a sample-size of 39 in each group.

## RESULTS

### Subjects

In total, 217 extremely preterm-born were admitted to the two NICUs during the three inclusion periods; 174 (80%) were alive at first follow-up. Survival rates at hospital discharge were 62%, 76% and 83% in the 82–85, 91–92 and 99–00 cohorts, respectively. During the follow-up period, three died and three were excluded due to inability to perform spirometry. In total, 148/174 (85%) participated at least once, 122/174 (70%) at two or more visits, and 99/171 (58%) participated at all possible visits (three for the 82–85 and 91–92 cohort, two for the 99–00 cohort) (figure 1). Sixteen subjects were included solely on the BW criterion, six in the 82–85 cohort (mean GA 31 weeks), two in the 91–92 cohort (GA 30 and 31 weeks), and eight in the 99–00 cohort (mean GA 29.6 weeks).

To recruit a full 1:1 control group, we approached 1.3 term-born subjects per extremely preterm-born in the 82–85 and 91–92 cohorts, and 1.6 in the 99–00 cohort. Altogether 138 controls were included, one died during the study period. In total, 93/137 (68%) participated at all possible visits and 115/138 (83%) at two or more visits.

## Perinatal characteristics

For term-born participants, mean BW increased with birth-decade. For extremely preterm-born, mean BW and GA decreased, and the proportion born SGA increased with birth-decade. Days on oxygen supplementation and the proportion with BPD increased with birth-decade, as did the use of CPAP, surfactant and antenatal as well as postnatal steroids, whereas the number of ventilator days decreased. Exogenous surfactant was unavailable for the 82–85 cohort, available as synthetic surfactant (Exosurf) provided according to the OSIRIS study protocol for the 91–92-cohort,<sup>22</sup> and as porcine-derived surfactant (Curosurf) provided according to existing guidelines to the 99–00 cohort. Details on neonatal management have been described previously.<sup>15 16</sup> Maternal smoking decreased with birth-decade. Perinatal characteristics did not differ between participants and non-participants in the 99–00 cohort, except that more non-participants were exposed to maternal smoking during pregnancy (56% vs 25%; online supplemental table E1). Non-participation rates for the two oldest cohorts were negligible (table 1).

## Anthropometric measurements and information from questionnaires

Adult extremely preterm-born attained a lower height than term-born. Questionnaires revealed no significant differences between the extremely preterm-born and term-born participants regarding wheeze, use of asthma medication or current asthma. Significantly more extremely preterm-born responded 'yes' to the question 'Have you ever had asthma', although atopy tended to be more common in term-born. Smoking became less common from the 82–85 to the 91–92 cohort for extremely preterm-born but not term-born ( $p < 0.001$  and  $p = 0.24$ , respectively). Complete questionnaire data from each visit are available in online supplemental table E2 (table 2).

## Lung function

For term-born controls, mean z-scores for spirometry variables were close to zero at most assessments (table 3). Notably, for the next-to last visit of the 99–00 cohort, mean z-FEV<sub>1</sub> was  $-0.3$  and the 95% CI did not include zero (table 3), thus, development was not completely stable over time (likelihood ratio test comparing a full model to a model without age effect for term-born,  $p = 0.005$ , figure 2).

For extremely preterm-born, mean z-scores for FEV<sub>1</sub>, FEV<sub>1</sub>/FVC and FEF<sub>25-75%</sub> were significantly below zero and below those of term-born at most assessments, with a few exceptions for the non-BPD group in the 91–92 and 99–00 cohorts (table 3). The deficits were largest for the BPD groups in the 82–85 and 91–92 cohorts. Within each of the extremely preterm-born cohorts, z-FEV<sub>1</sub> remained stable from childhood to adulthood (likelihood ratio test comparing a full model to a model without age effect for extremely preterm-born,  $p = 0.27$ , figure 2).

Significantly more extremely preterm-born than term-born had z-scores for FEV<sub>1</sub>, FEV<sub>1</sub>/FVC and FEF<sub>25-75%</sub> below LLN at minimum one visit (table 4). Notably, 44 (30%) extremely preterm-born compared with 7 (5%) term-born fulfilled the COPD spirometry criteria ( $p < 0.001$ ), with respectively 20 and 5 also reporting wheeze. The fraction below LLN for extremely preterm-born with vs without BPD were 24 (41%) vs 20 (22%), respectively.

**Table 1** Perinatal data

	82–85 cohort		91–92 cohort		99–00 cohort		P value
Term-born, participated/eligible	46/46		35/35		57/57		–
EP-born, participated/eligible	49/51		35/35		64/88		–
Perinatal data of term-born and EP-born subjects							
Birth weight in grams, mean (range)							
Term-born	3441	(3000–4000)	3564	(3010–4000)	3696	(2990–4500)	0.003
EP-born	1005	(580–1480)	933	(570–1400)	844	(450–1250)	<0.001
EP no BPD	1047	(580–1480)	976	(620–1400)	862	(450–1250)	0.001
EP BPD	888	(670–1080)	851	(570–1200)	827	(520–1100)	0.39
Maternal smoking during pregnancy, n (%)							
Term-born	10	(22)	9	(26)	–	(26)*	0.72
EP-born	22	(48)	13	(38)	15	(25)	0.06
Perinatal data of the EP-born subjects							
Gestational age in weeks, mean (range)	27.5	(23–34)	26.7	(23–31)	26.7	(24–31)	0.03
SGA, n (%)	9	(18)	5	(14)	23	(36)	0.03
Birth weight Z score, mean (SD)	–0.5	(1.2)	–0.3	(0.9)	–0.8	(1.3)	0.13
Postnatal days with oxygen treatment, median (quartiles)†	42	(26–56)	49	(26–71)	61	(40–78)	0.05
Days on CPAP, median (quartiles)	3	(0–14)	8	(1–28)	29	(19–42)	<0.001
Ventilator days, median (quartiles)	8	(1–16)	4	(1–12)	5	(2–9)	0.04
BPD n (%)	13	(27)	12	(34)	33	(52)	0.02
Antenatal steroids, n (%)	17	(35)	15	(44)	52	(81)	<0.001
Surfactant, n (%)	0	(0)	17	(49)	54	(84)	<0.001
Postnatal steroids, n (%)	4	(8)	10	(29)	20	(31)	0.01
PDA closure, medical or surgical, n (%)	13	(27)	17	(49)	14	(22)	0.02

Cohort differences were tested using Welch's one-way ANOVA for continuous variables and Pearson's  $\chi^2$  test for categorical variables.

\*Data not recorded for term-born from this cohort; the reported value represents percentage of smoking mothers of all births in the region, from the medical birth registry of Norway. The corresponding p value is based on comparison of the two earliest cohorts.

†Cohort differences were tested using Kruskal-Wallis test due to skewed data.

ANOVA, analysis of variance; BPD, bronchopulmonary dysplasia (supplemental oxygen or respiratory support at postmenstrual age  $\geq 36$  weeks); CPAP, continuous positive airway pressure; EP, subjects born extremely preterm or with extremely low birth weight (gestational age  $\leq 28$  weeks or birth weight  $\leq 1000$  g); PDA, persistent ductus arteriosus; SGA, small for gestational age (BW <10th percentile for GA according to Norwegian growth curves).

### Lung function differences across three decades

Across the three birth cohorts,  $z$ -FEV<sub>1</sub> for extremely preterm-born increased (likelihood ratio test comparing a model with a cohort effect for extremely preterm-born to one without a cohort effect,  $p=0.009$ ), and approached the term-born in the last cohort. The improvements occurred in the subgroup without BPD from the 1980s and in the subgroup with BPD from the 1990s (figure 2). When exploring effects from neonatal variables, only birth cohort and BW z-score had a significant impact on  $z$ -FEV<sub>1</sub> at 18 years ( $p=0.03$  and  $0.006$ , respectively), not maternal smoking, GA, BPD status, or the use of surfactant or antenatal steroids (online supplemental table E3). Current smoking was not associated with  $z$ -FEV<sub>1</sub> at 18 years ( $p=0.15$  and  $0.92$  for term and extremely preterm-born, respectively).

### Development of FEV<sub>1</sub> as percentages of peak expected values

FEV<sub>1</sub> expressed as percentages of expected adult peak values revealed parallel trajectories for term- and extremely preterm-born in the 82–85 and 91–92 cohorts (global test for lack of parallelism for these two cohorts,  $p=0.33$ ). In the 99–00 cohort, the trajectories diverged between the term- and extremely preterm-born (global test for lack of parallelism for all three cohorts,  $p=0.03$ ), with term-born developing marginally better. The two extremely preterm-born cohorts who had reached 25

years of age did not achieve their expected peak lung function, mean FEV<sub>1</sub>% of expected adult peak (95% CI) were 99% (96% to 101%) for term-born; 89% (84% to 94%) and 86% (83% to 90%) for extremely preterm-born in the 91–92 and 82–85 cohorts, respectively (figure 3).

From 25 to 35 years of age (82–85 cohort), FEV<sub>1</sub> declined for both term-born and extremely preterm-born. Relative to their expected peak values, the decline did not differ significantly between the groups (from 98.8% to 95.2% in term-born and 86.3% to 81.0% in extremely preterm-born, mean absolute difference in decline 1.7%, 95% CI (–2.2% to 5.7%),  $p=0.4$ ). FEV<sub>1</sub>% of expected peak values stratified by BPD status are presented in online supplemental figure E1.

### DISCUSSION

This is the first longitudinal population based study to report lung function trajectories from childhood to the mid-30s for extremely preterm-born cohorts, including also the incipient age-related physiological decline. FEV<sub>1</sub> tracked in parallel, but significantly below the trajectories of term-born controls, including a parallel peak and onset of the age-related decline from 25 to 35 years. Lung function deficits were most pronounced for those born extremely preterm in the early 1980s, and successively smaller for each succeeding decade of

**Table 2** Background variables (n=286)

Cohort	82–85 cohort			91–92 cohort			99–00 cohort		
Participated/eligible*	Term-born	46/46 (100)	–	35/35 (100)	–	57/57 (100)	–		
	EP-born	49/51 (96)		35/35 (100)		64/88 (73)			
Female sex, n (%), p value	Term-born	21 (46)	–	22 (63)	–	27 (47)	–		
	EP-born	21 (43)		22 (63)		31 (48)			
Final Height in cm, mean (SD), p value	Term-born	174 (8)	0.04	171 (9)	0.09	177 (10)		<0.001	
	EP-born	170 (8)		167 (9)		168 (10)			
Adult Weight in kg, mean (SD), p value	Term-born	73 (14)	0.73	73 (14)	0.34	73 (14)		0.02	
	EP-born	74 (18)		69 (14)		66 (14)			
Self-reported smoking, n (%), p value	Term-born	16 (35)	0.42	8 (23)	0.04	–†	–	–	
	EP-born	21 (43)		2 (6)		2 (6)			
Atopy, n (%), p value	Term-born	20 (43)	0.13	8 (23)	0.78	20 (40)		0.04	
	EP-born	13 (28)		9 (26)		12 (22)			
Wheeze last 12 months, n (%), p value	Term-born	17 (38)	0.27	15 (43)	0.34	7 (13)		0.10	
	EP-born	24 (49)		19 (54)		15 (24)			
Asthma med. last 12 months, n (%), p value	Term-born	6 (13)	0.34	4 (13)	0.17	3 (5)		0.25	
	EP-born	10 (20)		9 (26)		7 (11)			
Asthma ever, n (%), p value	Term-born	9 (20)	0.06	10 (29)	0.14	5 (9)		<0.001	
	EP-born	18 (37)		16 (46)		22 (35)			
Current asthma, n (%), p value	Term-born	6 (13)	0.10	8 (23)	0.29	4 (7)		0.31	
	EP-born	13 (27)		12 (34)		8 (13)			

The listed variables 'Allergy', 'self-reported smoking', 'wheeze last 12 months' and 'asthma med. last 12 months' refer to the number (fraction) with a least one positive response or finding at any visit. 'Current asthma' refers to a combination of wheeze in the last 12 months plus a positive response to the questions 'asthma ever' or 'asthma medication last 12 months' on minimum one visit. P value refers to comparisons between EP and term-born (Welch's t-test for continuous data and Pearson's  $\chi^2$  test for categorical data).

\*At least one visit (all percentage and p values are based only on visits where the subject participated).

†Data not presented due to large amount of missing data.

Adult weight, weight at 25 years (or 18 years if not applicable); Asthma med, asthma medication; EP, subjects born extremely preterm or with extremely low birth weight (gestational age  $\leq 28$  weeks or birth weight  $\leq 1000$  g); Final height, the height achieved at 18 or 25 years, whichever was highest.

birth. One in three extremely preterm-born participants met the spirometry criteria for COPD, although without prior administration of bronchodilator.

### Development of lung function from childhood to 35 years of age

Population studies underline the importance of intrauterine and early life events for adult peak lung function,<sup>23</sup> the starting point for physiological age-related decline. Even subtle reductions in adult FEV<sub>1</sub> are associated with cardiovascular disease, poor respiratory health, COPD, and overall mortality.<sup>24</sup> There is increasing awareness that COPD is a heterogeneous condition that originates early in life.<sup>25</sup> Until now, lifelong lung function trajectories for extremely preterm-born have represented uncharted territory, as no longitudinal studies have presented data beyond 25 years of age. This study highlights that a disturbingly high proportion individuals born extremely preterm commence their journey towards old age with FEV<sub>1</sub> levels significantly below normal, and that childhood and adolescent airway obstruction follow stable trajectories well into adulthood. This is in accordance with most longitudinal studies of younger extremely preterm-born cohorts,<sup>9 10 13</sup> although an Australian study reported deterioration of lung function from 8 to 18 years, most prominent in the BPD subgroup.<sup>11</sup> We observed an apparent decline in FEV<sub>1</sub> z-score from 25 to 35 years in our 82–85 BPD subgroup (figure 2), but this was not significant, possibly due to small sample size.

Extremely preterm-born harbour numerous risk factors known to be implicated in the development of COPD, such as bronchial hyper-responsiveness and early life lung infections.<sup>23 25</sup> As our spirometries were performed without prior bronchodilator and the questionnaires were not validated for assessing COPD symptoms, we could not classify COPD. Nevertheless, 30% of extremely preterm-born had FEV<sub>1</sub>/FVC below LLN, and 45% of these also reported wheeze in the ISAAC questionnaire. It was encouraging that the onset of the physiological lung function decline from 25 to 35 years did not differ between extremely preterm-born and term-born, suggesting that further age-related decline may not be as steep as reported for other high-risk groups.<sup>5</sup>

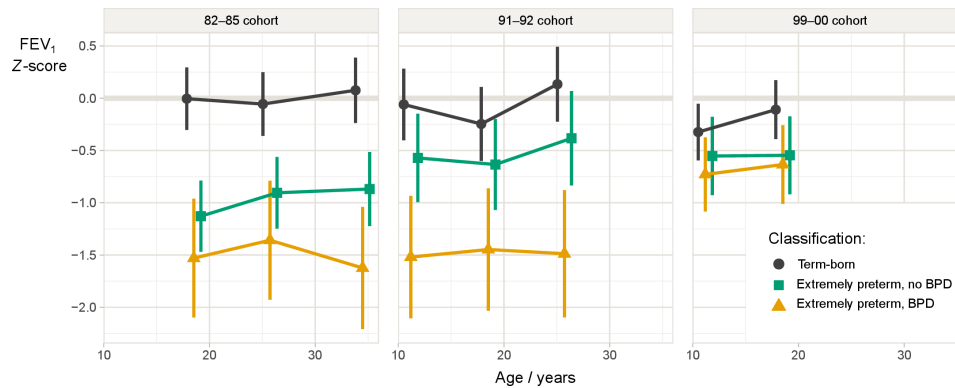
### Cohort effects associated with improved perinatal care

Neonatal intensive care improved substantially during the recruitment period, with more extensive use of prenatal steroids, introduction of surfactant, better respiratory care, and generally improved perinatal management.<sup>1</sup> Improvements in care may have contributed to increased survival for the most immature, but the long-term effects on morbidity are less obvious,<sup>26 27</sup> since a greater number of immature survivors conceivably could lead to poorer outcomes. The scarce literature on these matters is inconsistent. Doyle *et al* assessed three cohorts at 8 years of age born extremely preterm during 1991–2005, and found the poorest airflow patterns in the most recent cohort.<sup>28</sup> They argued this could be due to decreased use of postnatal corticosteroids

**Table 3 Spirometric lung function data comparing term-born with extremely preterm subjects (n=286 subjects)**

	82-85 cohort*			91-92 cohort			99-00 cohort											
Age (mean, range)	17.7 (15.3-19.9)	24.9 (22.5-27.0)	34.5 (32.1-37.6)	10.6 (9.7-11.5)	17.8 (17.0-19.2)	27.1 (26.1-28.4)	11.6 (10.1-13.8)	19.8 (18.2-21.4)										
n/eligible	46/46	40/46	34/46	35/35	28/35	26/34	54/57	43/57										
Term-born	34/38	32-33/38	25-26/36	23/23	19/23	15/23	26/43	27/43										
EP no BPD	12/13	12/13	9-10/12	12/12	12/12	9/12	32/45	23/45										
EP BPD																		
Mean	95% CI	P value <td>Mean <td>95% CI</td> <td>P value <td>Mean <td>95% CI</td> <td>P value <td>Mean <td>95% CI</td> <td>P value </td></td></td></td></td></td>	Mean <td>95% CI</td> <td>P value <td>Mean <td>95% CI</td> <td>P value <td>Mean <td>95% CI</td> <td>P value </td></td></td></td></td>	95% CI	P value <td>Mean <td>95% CI</td> <td>P value <td>Mean <td>95% CI</td> <td>P value </td></td></td></td>	Mean <td>95% CI</td> <td>P value <td>Mean <td>95% CI</td> <td>P value </td></td></td>	95% CI	P value <td>Mean <td>95% CI</td> <td>P value </td></td>	Mean <td>95% CI</td> <td>P value </td>	95% CI	P value							
<b>FEV<sub>1</sub> z-score</b>																		
Term-born (ref)	0.0	-0.3 to 0.3	-	-0.1	-0.4 to 0.3	-	-0.2	-0.6 to 0.1	-	0.1	-0.2 to 0.5	-0.3	-0.6 to -0.1	-	-0.1	-0.4 to 0.2		
EP no BPD	-1.1	-1.5 to -0.8	<0.001	-0.9	-1.2 to -0.5	<0.001	-0.6	-1.1 to -0.2	0.07	0.17	-0.8 to 0.1	-0.6	-0.9 to -0.2	0.33	-0.5	-0.9 to -0.2		
EP BPD	-1.5	-2.1 to -1.0	<0.001	-1.4	-1.9 to -0.8	<0.001	-1.5	-2.2 to -1.0	<0.001	<0.001	-1.4	-2.0 to -0.9	-1.5	-2.1 to -0.9	-0.6	-1.1 to -0.3		
<b>FVC z-score</b>																		
Term-born (ref)	-0.2	-0.5 to 0.1	-	0.0	-0.3 to 0.3	-	0.2	-0.2 to 0.2	-	0.4	0.1 to 0.8	-0.2	-0.4 to 0.1	-	0.0	-0.3 to 0.3		
EP no BPD	-0.9	-1.3 to -0.6	0.003	-0.4	-0.7 to 0.0	0.11	-0.3	-0.7 to 0.0	0.05	0.17	-1.0 to -0.1	-0.4	-0.9 to 0.0	0.41	-0.1	-0.5 to 0.3		
EP BPD	-1.1	-1.6 to -0.5	0.01	-0.6	-1.2 to 0.0	0.07	-0.9	-1.5 to -0.3	0.002	0.15	-1.2 to -0.1	-0.2	-0.8 to 0.4	0.95	-0.1	-0.7 to 0.2		
<b>FEV<sub>1</sub>/FVC z-score</b>																		
Term-born (ref)	0.4	0.1 to 0.6	-	-0.2	-0.4 to 0.1	-	0.1	-0.2 to 0.4	-	-0.1	-0.5 to 0.2	-	-0.5	-0.9 to -0.2	-	-0.3	-0.6 to 0.0	
EP no BPD	-0.3	-0.7 to 0.0	0.002	-0.9	-1.3 to -0.6	<0.001	-0.9	-1.3 to -0.5	0.004	0.73	-0.4 to 0.4	-0.3	-0.7 to 0.2	0.55	-0.5	-1.0 to -0.1	0.96	-1.2 to -0.4
EP BPD	-0.7	-1.2 to -0.1	0.001	-1.0	-1.6 to -0.5	0.007	-1.2	-1.8 to -0.6	0.003	<0.001	-1.4	-2.0 to -0.8	-1.7	-2.3 to -1.2	-1.9	-2.5 to -1.3	<0.001	-1.2 to -0.6
<b>FEF<sub>25-75%</sub> z-score</b>																		
Term-born (ref)	0.2	-0.1 to 0.5	-	-0.1	-0.4 to 0.2	-	-0.2	-0.6 to 0.1	-	-0.3	-0.7 to 0.0	-	-0.4	-0.8 to -0.1	-	-0.6	-0.8 to -0.3	
EP no BPD	-1.0	-1.3 to -0.7	<0.001	-1.2	-1.6 to -0.9	<0.001	-1.1	-1.5 to -0.8	<0.001	0.05	-1.2 to -0.4	-0.6	-1.0 to -0.2	0.32	-0.7	-1.1 to -0.2	0.35	-1.3 to -0.6
EP BPD	-1.5	-2.0 to -0.9	<0.001	-1.5	-2.0 to -0.9	<0.001	-1.6	-2.2 to -1.1	<0.001	<0.001	-1.9	-2.5 to -1.4	-1.9	-2.5 to -1.4	-2.1	-2.7 to -1.5	<0.001	-1.6 to -0.9

All results are based on longitudinal mixed-effects models. The p values compare EP subjects with controls. Two of the eligible non-participants could not be classified according to BPD status, but are presented in the non-BPD group. BPD, bronchopulmonary dysplasia (supplemental oxygen or respiratory support at postmenstrual age ≥36 weeks); EP, subjects born extremely preterm or with extremely low birth weight (gestational age ≤28 weeks or birth weight ≤1000 g); FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; ref, reference level.



**Figure 2** Estimated mean FEV<sub>1</sub> z-scores with 95% CIs in three cohorts of extremely preterm-born (born at gestational age ≤28 weeks or birth weight ≤ 1000 g) with or without BPD, and individually matched controls. BPD, bronchopulmonary dysplasia; FEV<sub>1</sub>, forced expiratory volume in 1 s.

or increased use of CPAP. We also observed increasing use of CPAP with birth cohort, however, no decrease in the use of postnatal steroids, which may have contributed to the differing results. Contrasting Doyle *et al* and in line with our findings, a meta-analysis addressing the effect of preterm birth on FEV<sub>1</sub> % suggested improvements with year of birth from 1980 to 1995.<sup>29</sup> One may even read a dose–response effect into our data-set, as improvements from the 1980s primarily occurred in those without BPD, presumably with the least traumatic neonatal history, whereas improvement from the 1990s also encompassed the BPD group (figure 2).

**Prospects for the future**

Advanced NICUs have facilitated survival in high numbers of immature infants for more than 30 years, paralleled by continuously refined treatment tools.<sup>2</sup> In our data set, these developments were paralleled by an apparent diminishing long-term significance of BPD. Instead, antenatal factors became more evident, reflected by negative effects from low BW z-scores, findings also reported in a recent Finnish study.<sup>30</sup> Preterm birth

happens for a reason, and the pathology that leads to early deliveries are likely implicated in the causal pathways that lead to subsequent pulmonary disease—irrespective of optimal post-natal care.

Huge efforts and resources are invested in acute perinatal care of extremely preterm-born compared with the resources spent on the long-term respiratory challenges that face adult NICU-graduates, with little evidence supporting that therapeutic interventions improve the pulmonary prognosis of BPD after discharge.<sup>31</sup> Notably, premature birth is not listed as a risk factor for COPD in authoritative statements, and data suggest that few pulmonologists inquire about early life factors.<sup>32 33</sup> Almost one in three extremely preterm-born participants met the post-bronchodilator spirometry criteria for COPD, and their upcoming age-related lung function decline will inevitably be a concern for adult pulmonologists. Thus, COPD after preterm birth appears to be a neglected condition, reflected even by the taxonomy; we still use the *neonatal* term BPD to label their adult lung disease—decades after their NICU discharge.

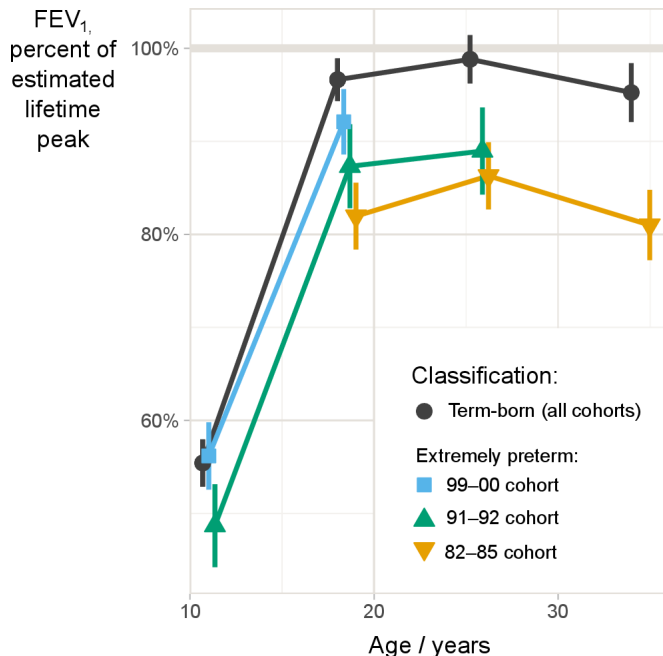
**Table 4** Spirometry variables below the lower limit of normal at any time

Cohort		82–85 cohort		91–92 cohort		99–00 cohort				
Z-FEV <sub>1</sub> below LLN at any time, n (%), p value	Term-born (ref.)	3	(7)	–	3	(9)	–	6	(11)	–
	EP no BPD	10	(28)	0.01	4	(17)	0.31	7	(23)	0.13
	EP BPD	7	(54)	<0.001	6	(50)	0.002	8	(24)	0.08
Z-FVC below LLN at any time, n (%), p value	Term-born (ref.)	3	(7)	–	0	(0)	–	4	(7)	–
	EP no BPD	8	(22)	0.04	2	(9)	0.08	1	(3)	0.46
	EP BPD	2	(15)	0.31	1	(8)	0.08	4	(12)	0.41
Z-FEV <sub>1</sub> /FVC below LLN at any time, n (%), p value	Term-born (ref.)	1	(2)	–	5	(14)	–	1	(2)	–
	EP no BPD	8	(22)	0.004	3	(13)	0.89	9	(29)	<0.001
	EP BPD	5	(38)	<0.001	9	(75)	<0.001	10	(30)	<0.001
Z-FEF <sub>25–75%</sub> below LLN at any time, n (%), p value	Term-born (ref.)	2	(4)	–	6	(17)	–	6	(11)	–
	EP no BPD	11	(31)	0.001	3	(13)	0.67	9	(29)	0.03
	EP BPD	7	(54)	<0.001	9	(75)	<0.001	12	(36)	0.003
Any variable below LLN at any time, n (%), p value	Term-born (ref.)	5	(11)	–	7	(20)	–	8	(14)	–
	EP no BPD	17	(47)	<0.001	6	(26)	0.59	12	(39)	0.008
	EP BPD	9	(69)	<0.001	10	(83)	<0.001	15	(45)	<0.001

The presented data are the number (fraction) of subjects with at least one value ≤LLN at least one visit.

P value refers to comparisons between term-born and EP-born groups using Pearson’s  $\chi^2$  test.

EP, subjects born extremely preterm or with extremely low birth weight (gestational age ≤28 weeks or birth weight ≤1000 g); FEF<sub>25–75%</sub>, forced expiratory flow at 25–75% of FVC; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; LLN, Lower limit of normal (z-score ≤ –1.645); ref., reference level.



**Figure 3** Mean measured FEV<sub>1</sub> as fraction of expected peak FEV<sub>1</sub> (with 95% CIs) in three population based cohorts born extremely preterm (born at gestational age  $\leq 28$  weeks or birth weight  $\leq 1000$  g) during three different decades (blue, green and yellow lines), and aggregated data for their individually matched term-born controls (black line), based on mixed-effects longitudinal model. Expected peak FEV<sub>1</sub> was calculated for each individual using the GLI reference equation. FEV<sub>1</sub>: forced expiratory volume in 1 s; GLI, global lung function initiative.

### Strengths and limitations

Strengths of this study were enrolment of three population-based cohorts born in three different decades, the longitudinal approach, relatively high follow-up rates, and free access to healthcare for all children in the recruitment area, reducing the risk of socioeconomic bias. Similar growth patterns drawn from multiple visits of three cohorts born in eras with different treatment opportunities, support the notion that lung function trajectories in extremely preterm-born parallel those of term-born. The same and unselected control groups throughout the study period minimised risks of selection bias. The senior NICU staff and senior members of the research group were largely the same throughout the study periods.

The main limitation was a relatively low number of participants; however, the population-based design ensured unbiased inclusion. The initial power analysis did not account for stratifying data by BPD or comparisons across cohorts, making subgroup analyses vulnerable to type II errors. GA was assessed by the last menstrual period during 1982–85 and by early ultrasound thereafter. We have previously shown that the different methods probably did not introduce significant bias.<sup>34</sup> Our extremely preterm-born cohorts were relatively mature at birth when compared with participants of other recent studies, such as the EPICure.<sup>10</sup> This was probably related to our inclusion criteria, also allowing participation of individuals with BW at or below 1000 g irrespective of GA, resulting in inclusion of more mature SGA infants. Thus, our outcome data are not directly generalisable to all extremely preterm-born cohorts. Categorising the long-term lung disease of preterms by their neonatal BPD status is debated. The definitions of BPD have

varied historically and between institutions, with no specific information on anatomy, mechanics, inflammation or pathology in the respiratory organs.<sup>35</sup> Due to the longitudinal design, we opted to stick with the ISAAC questionnaire throughout the study, although it is validated for children, not adults.<sup>18</sup> The 99–00 cohort were asked to respond to the questionnaires electronically at the last study-visit, unfortunately with lower response rates. Participation rates decreased over time and with more recent birth cohorts, but attrition did not exceed similar follow-up studies.<sup>36</sup> A higher rate of maternal smoking during pregnancy for those lost to follow-up in the 99–00 cohort may suggest that average outcomes were somewhat better in the participants. The spirometry results of the control groups largely confirmed that the GLI equations fitted our population, except the next-to-last visit for the youngest cohort where 95% CI for mean z-FEV<sub>1</sub> did not include zero. We have no clear explanation for this finding. This finding was most likely not attributable to the upgrading of spirometry equipment, as it did not apply to all control-cohorts. We therefore consider the risk of bias due to upgrading of equipment to be small, as laboratory standards were otherwise unchanged during the complete course of the study, and as spirometry is a robust technique.

### CONCLUSION

This is the first longitudinal study to describe lung function trajectories from childhood and well into adulthood for population-based cohorts of extremely preterm-born survivors. Spirometry variables tracked in parallel, but significantly below the trajectories of matched term-born controls, including a parallel peak and onset of the age-related decline from 25 to 35 years. On average, lung function deficits were most pronounced for participants born extremely preterm in the early 1980s, and successively smaller for each decade of birth. Irrespective of birth decade, almost one in three had spirometry values that met the spirometry criteria for COPD.

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informed consents from all participants and/or guardians. Participants gave informed consent to participate in the study before taking part.

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